Epirubicin chemotherapy in women with breast cancer: alternating arms for intravenous administration to reduce chemical phlebitis.

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Abstract:

Objective; To establish whether using alternating arms for peripheral intravenous epirubicin administration affects the severity or duration of epirubicin-induced phlebitis.

Methods; An observational study of females with breast cancer (n= 237) in a UK Cancer Centre. Data were analysed after receiving 3 treatment cycles according to the arm used for epirubicin administration: same, alternating, or mixed arm (2 consecutive cycles in one arm, one in the alternate arm). Phlebitis severity was graded by clinical staff after each treatment, participants also self-reported symptoms during treatment and for up to 6 months after.

Results: The alternating arms group experienced significantly less severe symptoms than the other arm use groups, 6% (4 of 64) compared to 34% ($p < 0.001$, odds ratio: 0.13 (95% CI: 0.043- 0.38) alternating arm compared to same arm group). The alternating arm group reported less pain ($p=0.013$), lower overall impact ($p= 0.009$) lower effect on function ($p= 0.032$) and shorter duration of symptoms ($p=0.001$) than the other arm use groups.

Conclusion: Using alternating arms for peripheral administration of epirubicin significantly reduces the severity and duration of chemical phlebitis and is recommended to improve patient experience and reduce the need for central venous access devices.

Key Words:

Epirubicin / breast cancer / chemotherapy / peripheral venous cannulation / chemical phlebitis / phlebitis severity

Introduction:

Breast cancer is the most frequently occurring cancer in women, affecting 2.1 million women worldwide each year (Bray *et al* 2018). In the UK breast cancer accounts for nearly a third of female cancers (Cancer Research UK, 2018) and approximately 34% of women with a primary diagnosis of invasive breast cancer will receive intravenous chemotherapy treatment (Cancer Research UK, 2018). Many will receive treatment with a combination of chemotherapy drugs including an anthracycline (such as epirubicin) as recommended by the National Institute for Health and Care Excellence Guidelines (NICE, 2018).

Epirubicin chemotherapy is known to cause phlebitis and venous sclerosis when administered through a peripheral cannula (Yamada *et al,* 2012). The reported incidence of epirubicin induced phlebitis varies considerably from 15 – 89% (Nagata *et al,* 2012; Lennan *et al* 2005) Phlebitis is defined as inflammation of a vein (Royal College of Nursing (RCN), 2016) and can be the consequence of chemical, mechanical or bacterial irritation of the tunica intima (Higginson and Parry, 2011). The phlebitis caused by epirubicin chemotherapy is due to chemical irritation and can result in a variety of symptoms including pain, arm tightness, swelling, redness, (Marshall-McKenna *et al*. 2015) and even puckering of the skin caused by sclerosis of the veins (Bolton-Maggs and Flavin 2005). These symptoms can last for more than 3 months post chemotherapy resulting in a considerable impact on the patient's quality of life and their ability to perform normal daily activities (Marshall-Mckenna *et al.* 2015). Furthermore, epirubicin is frequently administered in multi-drug combination chemotherapy regimens including 5-fluorouracil which can also cause phlebitis.

Concerns about the debilitating effect of phlebitis has resulted in the decision in at least one UK cancer centre to use peripherally inserted central venous catheters for all anthracycline chemotherapy (Harrold *et al.* 2015). This is currently not routine practice across the UK because of the small, but potentially serious complications of thrombosis and sepsis associated with central lines (LaRue and Peterson 2011, Gabriel 2013) as well as the significant financial and service implications.

It has been widely accepted practice for breast cancer patients following surgery to use the contralateral arm for all intravenous treatments. The rationale for avoiding venepuncture and cannulation of the ipsilateral arm following breast surgery is that it is thought to reduce the risk of developing lymphoedema. However, recent reviews have concluded that there is no convincing evidence for avoiding cannulation of the ipsilateral arm (Ferguson *et al* 2016, Jakes and Twelves 2015). The practice of repeated cannulation in the same arm has been shown by Uslusoy and Mete (2008) to increase the risk of phlebitis for surgical inpatients, but to date there are no reported studies looking specifically at patients receiving chemotherapy for breast cancer.

Following a review of the literature (Ferguson *et al* 2016; Jakes and Twelves 2015; Lennan and Richardson 2015; Cemal *et al* 2011) and consultation with the local lymphoedema specialist nurse a decision was made by the clinical team at Velindre Cancer Centre to recommend using alternate arms for chemotherapy administration in patients who had not undergone a full axillary node clearance. It was anticipated that alternating arms would reduce the incidence and severity of phlebitis in patients receiving combination chemotherapy including epirubicin at 3-weekly intervals.

The aim of this study was to establish if alternating the arm used for intravenous epirubicin administration over 3 cycles of chemotherapy would affect the severity or duration of epirubicin-induced phlebitis.

Methods:

A prospective observational study was used to collect clinical staff and participant assessments of phlebitis symptom severity following three cycles of chemotherapy containing epirubicin administered at 3-weekly intervals.

The study population comprised women with breast cancer receiving combination chemotherapy including epirubicin (Table 1) via a peripheral cannula (for inclusion and exclusion criteria see Table 6). Participants were recruited from Velindre Cancer Centre, Cardiff between May 2016 and January 2018, and from Aneurin Bevan University Health Board, South East Wales between October 2016 and November 2017. Participants in both locations were treated by Velindre Cancer Centre nursing staff following the Cancer Centre guidelines. Chemotherapy was administered through a 24g cannula for all participants and epirubicin was administered by experienced chemotherapy nurses as a bolus into the injection port on the tubing of a free running intravenous infusion of 0.9% saline. The study received local ethical approval (REC reference: 16/WA/0074) and written informed consent was obtained from all participants. Participant characteristics and treatment-related information was collected from medical records and a baseline participant questionnaire.

Following the Cancer Centre guidelines participants who had undergone a sentinel node biopsy (SNB), or were receiving neo-adjuvant chemotherapy prior to surgery, were free to choose (after discussion with the clinical team) which arm, or combination of arms to use for chemotherapy administration. There was no imposed randomisation of arm to use, or control of which arm (the ipsilateral or contralateral) to use first. Following local guidelines those who had undergone an axillary node clearance (ANC) were advised to only use the contralateral arm for chemotherapy.

Participants could be divided into five groups according to the sequence of arm chosen for epirubicin administration. The possible sequences of arm used over 3 cycles were 1) same arm for each treatment due to ANC; 2) same arm without ANC; 3) alternating arms; 4) first 2 cycles in one arm then the 3rd cycle in the alternate arm and 5) first cycle given in one arm followed by 2 cycles in the alternate arm

A chemotherapy phlebitis severity assessment tool developed by Velindre Cancer Centre with an inter-rater reliability of 89% was used to grade symptoms from 0 (no symptoms) to 4 (severe symptoms) (Figure 1). Assessments were performed by clinical staff at the chemotherapy clinic review approximately 3 weeks post treatment. After each treatment cycle participants were asked to complete a short questionnaire (see *supporting information*) designed to allow self-reporting of the severity and impact of any symptoms experienced.

Participants also completed a follow up self- assessment questionnaire once every 3-4 weeks if they still had symptoms on completion of epirubicin chemotherapy. The questionnaire was completed either face to face, by telephone or on-line depending on patient preference and whether they had a pre-planned hospital attendance.

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A Chi Square test was used to identify differences between groups. Statistical significance was set at 0.05. Statistical Package for Social Science V25 (USA) software was used to make the comparisons.

Results:

Participant characteristics and arm use groups

Complete data for three cycles was collected from 90% (237 of 263) of the women recruited with a mean age of 54 (±10) and a mean BMI of 29 (±6). 214 (90%) were Caucasian, 134 (10%) participants described themselves as current smokers, 79 (33%) as previous smokers and 134 (57%) had never smoked. 147 participants (62%) received 75mg/m^2 of epirubicin, 85 (36%) received 100mg/m^2 and 5 (2%) 60mg/m^2 (Table 2). Assessment data were not complete for 2 women, and 24 did not receive three cycles of epirubicin peripherally; of these 4 continued treatment with a central venous catheter, epirubicin was stopped after cycle 1 for two participants and after cycle 2 for the remaining 18.

There was no significant difference (p = 0.51) in the severity of symptoms experienced between the two same arm groups (ANC and non-ANC) so they were combined to form a single group (Group1, Table 2). Forty six percent (108 of 237) of the participants received all three cycles of chemotherapy in the same arm. Alternating arms were used in 64 (27%) cases. No significant difference (p = 0.59) could be demonstrated between sequences 4 and 5 so they were also combined as the mixed arm use group, 65 (27%) received two consecutive cycles in one arm and one cycle in the alternate arm (Group 3, Table 2).

No differences in the dose of epirubicin or key baseline characteristics other than a significant difference in axillary surgery between the same arm group (Group 1, Table 2) and the other arm use groups (Groups 2 and 3, Table 2) were noted. The higher proportion of participants in Group 1 with ANC was expected as these were advised to avoid chemotherapy administration in the ipsilateral arm so were anticipated to receive all treatments in the same arm.

Staff assessment of symptoms during epirubicin

Using the Chemotherapy Induced Phlebitis Severity (CIPS) scale (Figure 1) to assess participants after 3 cycles of epirubicin chemotherapy there was a significant difference in the severity of symptoms between the arm use groups (p=<0.001). Approximately a third of participants (34%), in the same arm group (37 of 108) and the mixed arm group (22 of 65) experienced the more severe grades 3 or 4 phlebitis compared to 6% (4 of 64) in the alternating arm group (Table 3) leading to an odds ratio for experiencing high grade symptoms of 0.12 (95% CI: 0.043- 0.38) compared to the same arm group. The odds ratio for most severe symptoms for the mixed arm group compared to the same arm group is 0.98 (95% CI: 0.51 -1.88). The alternating arm use group also demonstrated a higher proportion of participants who experienced no symptoms (16 of 64: 25%) compared to the same arm group (11 of 108: 10%) and the mixed arm use group (4 of 65: 6%).

Participant reported symptoms during epirubicin

The self-reported questionnaires showed that there was a significant difference between arm use groups, with the alternating arm group consistently reporting a lower severity of symptoms for all three patient reported measures than either the same arm or mixed arm

use groups (Table 4). The number of participants reporting severe symptoms was small so moderate and severe symptoms were grouped together for analysis. The alternating arm group reported significantly less pain (p = 0.013), significantly lower levels of overall impact (p = 0.009) and significantly lower effect on function (p = 0.032).

Dose of epirubicin

Analysis of the severity of symptoms experienced for all participants by epirubicin dose demonstrated that there was a significantly higher proportion of grade 3 and 4 symptoms in those who received 100mg/m^2 (p=0.023) compared to those receiving lower doses (Table 5). A further analysis by arm use group demonstrated that the alternating arm group experienced less severe symptoms at all doses, with a significantly lower proportion of grade 3 and 4 symptoms at the lower doses (p=0.005) and at 100mg/m^2 (p= 0.025).

Combination regimen comparison

The chemotherapy regimen administered for the first 3 cycles was a combination of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) for 93% (221 of 237) of the participants, and 7% (16 of 237) received the combination of epirubicin and cyclophosphamide (EC). There was no significant difference in the proportion of participants experiencing grade 3 and 4 symptoms when comparing those who had received FEC with those who had received EC (p=0.249). An additional analysis by arm use group for the 221 participants who had received FEC demonstrated that the alternating arm group experienced significantly less grade 3 and 4 symptoms than the other arm use groups (p=0.01).

Symptoms after completion of epirubicin chemotherapy.

Participants with any symptoms on completion were followed up either until the symptoms resolved, or for a maximum of 6 months. Complete follow up data using participant questionnaires to self-report symptoms were recorded for 73% (172 of 237) participants (Figure 2). There was a significant difference between arm use groups when comparing how long participants experienced symptoms after completion of chemotherapy (p=0.001). The alternating arm group had a significantly higher proportion completing the study with no symptoms requiring follow up (17 of 41: 41%) and a lower proportion still reporting symptoms after the maximum 6 months follow up (3 of 41: 7%) compared with the other groups. There was no significant difference between the same arm and mixed arms use groups.

Discussion:

Guidelines for administration of intravenous medication (RCN, 2016) recommend that central venous catheters (CVC) should be considered for the administration of drugs such as epirubicin with a low pH (<5) which are thought to have an increased potential for causing chemical phlebitis. However, the evidence base for this guidance has been questioned by Gorski *et al* (2015) who concluded that the pH of the drug cannot be used in isolation as basis for using a CVC. Yamada *et al* (2012) in their study of epirubicin-induced vascular injury also state that the mechanism of epirubicin-induced phlebitis is not definitely pH related. The proactive placement of CVCs for epirubicin chemotherapy is reported as common practice in the US (Marshall-Mckenna *et al,* 2015) but is not routine practice in

many areas of the UK. Harrold *et al* (2015) reported on a decision in one UK oncology centre to place peripherally inserted central catheters (PICC) for all breast cancer patients being treated with anthracycline chemotherapy (including epirubicin) but acknowledged that they were unable to identify any national recognised best practice guidelines to support this. Le Vasseur *et al* (2018) also identified concerns at the lack of consensus for best practice, and the absence of research directly comparing peripheral and central venous access for chemotherapy administration in breast cancer.

After 3 cycles of epirubicin 87% (206 of 237) of participants experienced phlebitis of any grade, however only 27% (63 of 237) experienced grade 3 and 4 symptoms which result in pain and interfere with arm function. The lower grade symptoms were viewed by participants as being a minor inconvenience and did not require clinical intervention. Elsewhere the reported incidence of epirubicin- induced phlebitis varies considerably; Nagata *et al* (2012) reported rates as low as 15% in 26 patients following a change in administration technique and formulation of epirubicin which is lower than the total rate of phlebitis of 87% in this study. Our reported rate is similar to the 89% reported by Lennan *et al* (2005) in their audit of 19 patients, and the incidence of up to 71% in the retrospective audit of 110 patients conducted by Marshall-McKenna *et al* (2015). It is difficult however to make any meaningful comparisons with the study data due to differences in methodology, small scale studies and use of retrospective data collection.

A potentially confounding factor in this study was the inclusion of participants who had received different combination regimens, 7% (16 of 237) received combination chemotherapy without 5- fluorouracil (5-FU). The chemotherapy drug 5-FU is also known to cause phlebitis and could have potentially influenced the incidence and severity of phlebitis however the phlebitis resulting from 5-FU is most commonly seen with prolonged infusions rather than the bolus administration used for this study (Gebbia *et al* 1999) and although 5-FU is a venous irritant it is usually associated with superficial phlebitis symptoms (Berardi *et al* 2003) without the more severe venous sclerosis resulting from the vesicant epirubicin. Zhang *et al* (2016) demonstrated that the incidence of phlebitis was significantly lower when epirubicin and cyclophosphamide were given in combination with capecitabine (an oral pro-drug of 5-FU) instead of intravenous 5-FU. However, the TACT-2 study with over 4,000 participants (Cameron *et al* 2017) demonstrated no significant difference in the rates of phlebitis when comparing the combination of intravenous cyclophosphamide, methotrexate and 5FU with oral capecitabine (both administered after four cycles of epirubicin). The results of our study support the findings of Cameron *et al* (2017) with no significant difference in the severity of phlebitis ($p=0.249$) between those receiving epirubicin in combination with 5-FU and compared to those who did not receive 5-FU.

Using a CVC could potentially have prevented the distressing higher-grade symptoms experienced by 27% of our participants. However, as we were unable to predict who will experience the higher-grade symptoms the routine use of CVC would have resulted in 73% (174 of 237) of participants who experienced no or low-grade symptoms undergoing the placement of a CVC for no clear clinical benefit. CVCs are associated with an increased risk of infection and thrombosis (Beckers *et al,* 2010), along with the potential for delay in commencing treatment, increased costs of placement and follow up care. Therefore, there should be a clear evidence-based rationale for the decision to place a CVC, particularly for patients receiving chemotherapy who are at an increased risk of potentially life-threatening infection and thrombosis (Noble and Pasi, 2010).

Uslusoy and Mete (2008) identified that rates of phlebitis are higher when repeatedly using the same arm for intravenous medication, and alternating arm administration is recommended as best practice to preserve veins for prolonged courses of intravenous therapy (Weinstein, 2007). However, for many years patients with breast cancer have received all chemotherapy treatments in the contralateral arm, increasing the risk of significant phlebitis and venous sclerosis. The advice to avoid all medical procedures in the arm on the side of breast surgery including venepuncture, cannulation and even blood pressure monitoring has arisen from concerns about increasing the risk of developing lymphoedema. The evidence base for this practice is poor and has even been described as anecdotal (Ferguson *et al,* 2016). The most recent guidance from National Institute for Health and Care Excellence guidance (NICE, 2018) confirms the lack of evidence for any increased risk of lymphoedema following medical procedures including injections on the surgical arm and advices that decisions about using the ipsilateral arm should be made depending on clinical need.

Our study demonstrates that alternating arm use is associated with a significant reduction in the proportion of participants experiencing severe symptoms of chemical phlebitis. Severe grade 3 and 4 symptoms were experienced in only 6% of those using alternating arms compared to 34% in the two other arm use groups ($p = <0.001$). There was a clearly observed association between the dose of epirubicin and the severity of symptoms with a higher incidence of grade 3 and 4 symptoms for those who received higher doses of epirubicin ($p=0.023$). However alternating arm use resulted in a significantly lower incidence of high-grade symptoms at doses of 100mg/m^2 with 10% of the alternating arm group experiencing grade 3 or 4 symptoms compared to 42% in the same arm group, and 45% in the mixed arm use group ($p= 0.025$). These results indicate that peripheral administration of epirubicin chemotherapy can be safely delivered even at higher doses if alternating arms are used. However, it is recommended that a CVC should be considered for patients receiving doses of 100mg/m^2 where alternating arms cannot be used, or who have poor venous access. In our study alternating arms for chemotherapy administration was recommended only for patients who had not undergone a full axillary node clearance. The 2018 NICE guidance advises that patients should be informed that there is no additional risk of lymphoedema if the ipsilateral arm is used for intravenous drug administration and does not distinguish between ANC and SNB. Therefore, consideration should also be given to offering the choice of alternating arms to all women with breast cancer including following an ANC, this could further reduce the need for CVC placement.

There was no difference in the proportion of participants experiencing severe symptoms between the same arm group and mixed arm group. This would suggest that the administration of at least two consecutive cycles in the same arm is a key factor in the development of higher-grade phlebitis. Participants in the alternating arm group frequently reported a delayed onset of symptoms which occurred approximately five weeks after chemotherapy was last administered. Webster *et al* (2015) identified that phlebitis results from an inflammatory response and therefore symptoms of post-infusion phlebitis commonly present late. Hegerova *et al* (2015) also reported a delayed onset of phlebitis following doxorubicin chemotherapy with symptoms appearing on average 22 days after treatment. There is thus a cumulative effect with increased venous irritation and higher-grade symptoms occurring when consecutive cycles are administered in the same arm. This can be seen with the increasing severity of symptoms from cycle 1 to 3 with only two

participants (1%) experiencing higher grade symptoms after cycle 1 compared to 54 (23%) after cycle 3.

It was observed that many of the participants in the mixed arm group (Group 3) chose to swap to the alternate arm for cycle 3 after two consecutive cycles in the same arm had resulted in developing more severe symptoms. This reflects the initial reluctance of both staff and patients to change practice due to historical concerns about the risk of lymphoedema. It was noted that the proportion of participants who had not undergone ANC who received chemotherapy in alternating arms increased from 25% in the first 6 months of recruitment to 65% in the final 6 months. This demonstrates the time taken for this change to be embedded in practice, acceptance of the recommendations required consistent information and explanation to both staff and patients. However there remains some resistance to the change reflecting how deeply engrained the beliefs about lymphoedema risk are, despite the lack of evidence.

No recommendations were made concerning the sequence of arm use, however it was interesting to note that in the alternating arm group 90% (35 of 39) of those who had undergone breast surgery received only 1 cycle in the surgical arm, and 65% (13 of 20) of those undergoing neo-adjuvant chemotherapy received only 1 cycle in the arm on the side affected. This would suggest a deliberate choice to use the ipsilateral arm only once. It is not known if this was a result of patient choice, guidance from the clinical team or a combination of factors.

There was also a significant difference in the duration of symptoms reported by participants after completion of epirubicin chemotherapy with approximately a third of the same arm and mixed arm use groups still reporting symptoms 6 months after completion of treatment compared to 10% of the alternating arm group ($p=0.001$). Participant comments reflected the considerable negative impact of ongoing symptoms of pain and arm tightness on their daily activities and how the visible scarring of veins affected their body image (Figure 3).

Study Limitations

This study was undertaken for patients under the care of one UK Cancer Centre it was an observational study, neither blinded or randomised for arm use. Data analysis was based on 3 cycles as the number of participants completing 6 cycles was small (not reported). The follow up survey of phlebitis symptoms were self-reported and thus are likely to be more variable than those reported by staff.

Conclusion:

Peripheral cannulation which is inexpensive, minimally invasive and does not require any ongoing care remains the primary venous access choice for many areas for epirubicin administration despite the risk of chemical phlebitis. There is therefore a need to identify who is most at risk of epirubicin- induced phlebitis and whether administration techniques can reduce the incidence. Although intravenous access guidance suggests that irritant drugs such as epirubicin should be ideally administered through a central line, 73% of participants in this study did not experience significant symptoms and where alternating arms were used this number increased to 94%. This study has clearly demonstrated that women with breast cancer who used alternating arms for peripheral administration of epirubicin experienced a significant reduction in severity and duration of chemical phlebitis.

Decisions about venous access choices should be made after an informed discussion with the patient based on evidence. This study has helped to provide evidence to inform discussions with patients when making choices about venous access for epirubicin chemotherapy. However more studies are required for a better understanding of the risk factors for epirubicin-induced phlebitis to enable a fully informed discussion with patients about their individual risk and whether they would benefit from a CVC.

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Tables

Table 1: Combination chemotherapy regimens including epirubicin used to treat participants

Regimen	Drugs	Dose	Usual number of cycles	Number of participants
FEC	5 Fluorouracil Epirubicin Cyclophosphamide	600mg/m^2 60 or 75mg/m^2 600mg/m^2	6 cycles	56
FEC -T	5 Fluorouracil Epirubicin Cyclophosphamide Docetaxel (Taxotere™)	600mg/m^2 60, 75 or 100mg/m^2 600mg/m^2 75mg/m^2	3 cycles FEC folllowed by 3 cycles Docetaxel	165
EC	Epirubicin Cyclophosphamide	60, 75 or 100mg/m^2 600mg/m^2	4 or 6 cycles	16

Table 2: Key patient and treatment characteristics by arm use group

		Group 1: n= 108 Same arm	**Group 2: n= 64** Alternating arms	**Group 3: n= 65** Mixed arms
	Age (years)[#]	55 ± 10	55 ± 12	51 ± 12
	BMI[#]	29 ± 6	29 ± 6	29 ± 6
Smoking history	Never smoked	59 (55%)	39 (61%)	36 (55%)
	Previous smoker	35 (32%)	20 (31%)	24 (37%)
	Current smoker	14 (13%)	5 (8%)	5 (8%)
Axillary surgery	None	1 (1%)	22 (34%) *	21 (32%)
	Sentinel node biopsy (SNB)	20 (19%)	39 (61%) *	43 (66%)
	Axillary node clearance (ANC)	87 (81%)	3 (5%) *	1 (2%)
Baseline albumin g/l	< 35	9 (8%)	5 (8%)	7 (11%)
	≥ 35	99 (92%)	59 (92%)	58 (89%)
Epirubicin dose mg/m^2	60	2 (2%)	2 (3%)	1 (2%)
	75	63 (58%)	42 (66%)	42 (65%)
	100	43 (40%)	20 (31%)	22 (34%)
Ethnic group	White	96 (89%)	59 (92%)	59 (92%)
	Non-white	8 (7%)	2 (3%)	2 (3%)
	Missing data	4 (4%)	3 (5%)	4 (6%)

[#]Mean ± SD shown. See text for groups. * p =< 0.05 X^2 test: Group 2 compared to Groups 1&3, otherwise no significant differences were observed between groups.

Table 3: Graded severity of symptoms in each arm use group after 3 cycles of epirubicin chemotherapy.

	Group 1: n= 108 Same arm	**Group 2: n= 64** Alternating arms	**Group 3: n= 65** Mixed arms
Grade 0: n (%)	11 (10)	16 (25) *	4 (6)
Grade 1&2: n (%)	60 (56)	44 (69)	39 (60)
Grade 3&4: n (%)	37 (34)	4 (6) *	22 (34)

* p =< 0.05 X^2 test: Group 2 compared to Groups 1&3, otherwise no significant differences were observed between groups.

Table 4; Participant reported symptoms after 3 cycles of epirubicin

		Group 1: n= 108 Same arm	**Group 2: n= 64** Alternating arms	**Group 3: n= 65** Mixed arms
Pain: n (%)	None	17 (16)	21 (33) *	10 (15)
	Mild	43 (40)	27 (42)	23 (35)
	Moderate + severe	36+9 (42)	14+1 (23) *	25 +7 (49)
	Missing	3 (3)	1 (2)	0
Overall impact: n (%)	None	51 (47)	48 (75) *	34 (52)
	Mild	29 (27)	11 (17)	20 (31)
	Moderate + severe	24+1 (23)	5+0 (8) *	11+0 (17)
	Missing	3 (3)	0	0
Effect on arm function: n (%)	None	61 (56)	50 (78) *	38 (58)
	Mild	30 (28)	13 (20)	18 (28)
	Moderate + severe	14+0 (13)	1+0 (2) *	8+0 (12)
	Missing	3 (3)	0	0

* p =< 0.05 X^2 test: Group 2 compared to Groups 1&3, otherwise no significant differences were observed between groups.

Table 5: Symptom grade by arm use group and dose of epirubicin

	60 & 75mg/m^2 (n=152)			**100mg/m^2 (n= 85)**	
	Grades 0,1 & 2	Grades 3 & 4		Grades 0,1 & 2	Grades 3 & 4
Group 1: Same arm **(n= 65)**	46 (71%)	19 (29%)	**Group 1:** Same arm **(n=43)**	25 (58%)	18 (42%)
Group 2: Alternate arms **(n=44)**	42 (95%) *	2 (5%) *	**Group 2:** Alternate arms **(n=20)**	18 (90%) *	2 (10%) *
Group 3: Mixed arms **(n=43)**	31 (72%)	12 (28%)	**Group 3:** Mixed arms **(n=22)**	12 (55%)	10 (45%)

* p =< 0.05 X^2 test: Group 2 compared to Groups 1&3, otherwise no significant differences were observed between groups.

Inclusion criteria	**Exclusion criteria**
• Breast cancer diagnosis – primary, secondary or recurrence • Age 18 years or over • Female • Planned to receive anthracycline chemotherapy • Chemotherapy planned to be given via a peripheral venous cannula • Assessed as medically fit to receive anthracycline based chemotherapy	• Pregnant • Male • Under 18 years old • Unable to provide informed consent • For chemotherapy not including an anthracycline • Chemotherapy planned to be given through a central venous catheter • Assessed as not medically fit for anthracycline chemotherapy.

Table 6: inclusion and exclusion criteria

Figures

Chemotherapy Induced Phlebitis Severity Scale

Canolfan Ganser Felindre
Velindre Cancer Centre

Grade	Description of arm symptoms
0: None	No symptoms
1: Mild	**One or more** of the following are present: • Mild pain or tenderness • Redness at cannula site < than 5cms • Vein discolouration/ streak formation • Tethering* of skin along the vein **No** swelling **No** palpable venous cord** **No** effect on ADL***
2: Moderate	**One** of the following is present: • Moderate pain • Palpable venous cord • Redness > than 5cms along the vein **No** swelling. **No** significant effect on ADL
3: Marked	**Two or more** of the following are present: • Moderate pain • Palpable venous cord • Redness >5cms along the vein • Swelling • Arm symptoms make some ADL much more difficult or painful
4: Severe	**Two or more** of the following are present: • Severe pain • Palpable venous cord • Obvious signs of infection eg redness, swelling and heat • Arm symptoms limit ability to carry out many ADL • Inability to use arm for further chemotherapy

***Tethering**: visible puckering or dimpling of the skin along the vein, or a feeling of tightness.
****Venous cord**: a palpable, hard tracking along the length of vein
*****ADL:** activities of daily living

As a guide to pain assessment use a Likert scale to score pain severity from 1 -10:

0 1 2 3 4 5 6 7 8 9 10

1 -3 = mild pain | **4-7 = moderate pain** | **8 -10 = severe pain**

Figure 1; Chemotherapy Induced Phlebitis Severity scale (CIPS)

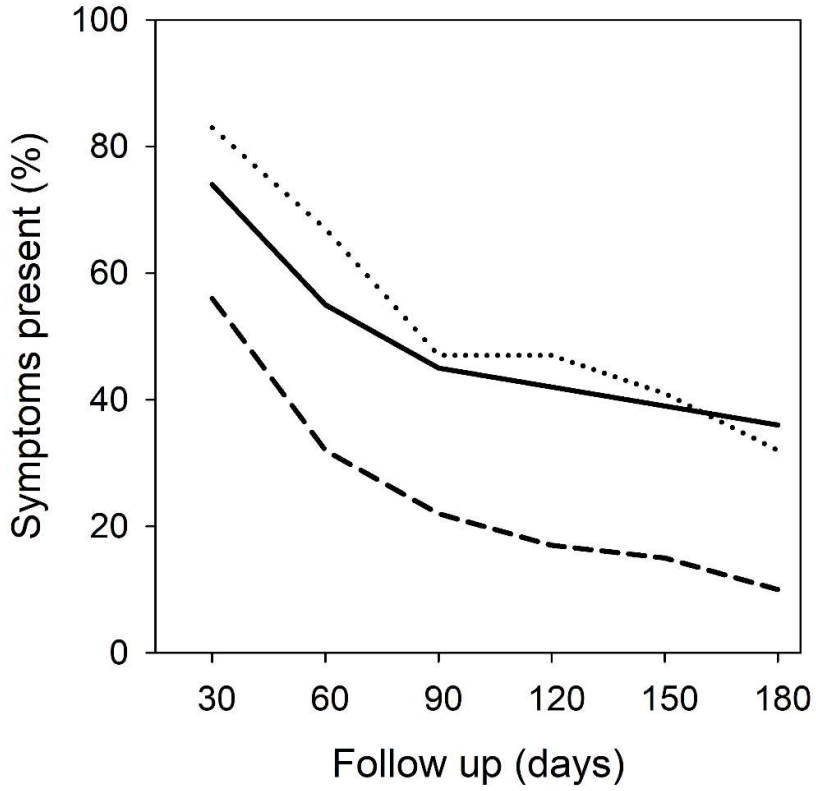

Figure 2: Proportion of participants reporting symptoms during follow up

— Group 1: same arm; ----- Group 2: alternate arms; ····· Group 3: mixed arms.

Arm aches after doing activities such as hanging out washing. Washing up putting cleaner over. Feels like a trapped nerve in upper arm causing discomfort all down arm (AA150)

Can't carry anything on forearm anymore (AA060)

The puckering is still visible from my wrist to past my elbow and I am worried about how it looks wearing short sleeves heading into the summer (AA252)

Will the puckering and pain eventually disappear? (AA268)

Even after 4months since my last chemo, I still experience pain in the lower right arm, around the veins and the puckering when I straighten the arm is still a lot. (AA118)

I guess that as it's been nearly four months since the treatment finished, the puckering is now permanent. This makes me very sad. (AA140)

Figure 3: Participant comments reflecting the impact of symptoms post chemotherapy